REMARKS

Amendments

Claims 1-3, 8-11, 15-19, 23, 25, 27, 28, 30, 32, and 33 have been amended to place the claims in accordance with U.S. patent practice. The dependencies of claims 8, 10-15, 18-23, and 27-32 have been amended and, as a result, new claims 43-63 have been added to avoid the occurrence of an improper multiple dependency. Exemplary embodiment have been deleted from claims 2-3, 15, 23, and 32 and presented as new claims 41-42, 47-49, 54-56, and 61-63. Support for these amendments is provided in the following table:

New Claim	Supported by originally-filed claim(s)	Support for new claim in specification
41	2-3	p. 6- p. 11
42	8	p. 30, lines 1-5
43	11	p. 27, lines 8-13
44	12/11	p. 27, l. 15- p. 28, l. 4
45	13/11	p. 29, lines 7-10
46	14/11	p. 29, lines 7-10
47-49	15	p. 30, lines 1-5
50	19	p. 27, lines 8-13
51	20/19	p. 27, l. 15- p. 28, l. 4
52	21/19	p. 29, lines 7-10
53	22/19	p. 29, lines 7-10
54-56	23	p. 30, lines 1-5
57	28	p. 27, lines 8-13
58	29/28	p. 27, l. 15- p. 28, l. 4
59	30/28	p. 29, lines 7-10
60	31/28	p. 29, lines 7-10
61-63	32	p. 30, lines 1-5

Claims 10, 18, and 27 have been rewritten to depend only upon the compound of claim 2 or 3. Additionally, claim 30 has been amended to correct an error in the claim's dependency. Claims 24 and 34-40 have been canceled.

No new matter is introduced by any of the amendments herein.

Claims 1-3, 8-11, 15-19, 23, 25, 27, 28, 30, 32, and 33 -Version With Markings to Show Changes Made:

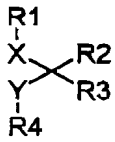
1. A pharmaceutical formulation, comprising:

(i) an inhibitor of carboxypeptidase U or a pharmaceutically acceptable salt thereof; **[**,**]** and

(ii) a thrombin inhibitor or a derivative thereof,

in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier.

2. The pharmaceutical formulation according to claim 1, wherein the inhibitor of carboxypeptidase U is a compound of general formula I



(I)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein:

R_1 is selected from the group consisting of: **[**represents,**]**

C_1-C_6 alkyl, substituted with one or more basic groups **[**such as amino, amidino and/or guanidino**]**;

cycloalkyl, substituted with one or more basic groups **[**such as amino, amidino and/or guanidino**]**;

heterocyclyl, comprising **[**containing**]** at least one nitrogen atom;

heterocyclyl, comprising **[**containing**]** at least one hetero atom selected from S or O, and substituted with one or more basic groups **[**such as amino, amidino and/or guanidino**]**; and

[or**]** aryl, substituted with one or more basic groups; **[**such as amino, amidino and/or guanidino,**]**

R_2 is selected from the group consisting of [represents] H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O, ZO-CO-NZ-, and [or] Z_2N-CO-NZ-; [group,]

R_3 is selected from the group consisting of [represents] $COOR_5$, $SO(OR_5)$, SO_3R_5, $P{=}O(OR_5)_2$, $B(OR_5)_2$, $P{=}OR_5(OR_5)$, [or] tetrazole, and a [or any] carboxylic acid isostere; [,]

R_4 is [represents] SH, S-CO-C_1-C_6 alkyl, or S-CO-aryl; [,]

R_5 is [represents] H, C_1-C_6 alkyl, or aryl; [,]

R_6 is [represents] H or C_1-C_6 alkyl; [,]

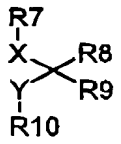
X is selected from the group consisting of [represents] O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_6SO_2, SO_2NR_6, NR_6CO, and [or] $CONR_6$; [,]

Y is [represents] $C(Z)_2$; and [,]

Z is [represents] independently selected from the group consisting of H, C_1-C_6 alkyl, aryl, cycloalkyl and [or] heterocyclyl.

3. The pharmaceutical formulation according to claim 1, wherein the inhibitor of carboxypeptidase U is a compound of general formula II,

[(ii) a compound of general formula II]



(II)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein:

R_7 is selected from the group consisting of: [represents,]

C_1-C_6 alkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

cycloalkyl, substituted with one or more basic groups [such as amino, amidino and/or guanidino];

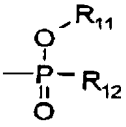
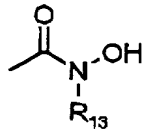
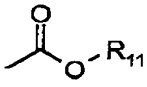
heterocyclyl, comprising [containing] at least one nitrogen atom;

heterocyclyl, comprising [containing] at least one hetero atom selected from S or O, and substituted with one or more basic groups [such as amino, amidino and/or guanidino]; and

[or] aryl, substituted with one or more basic groups; [such as amino, amidino and/or guanidino,]

R_8 is selected from the group consisting of [represents] H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, a Z_2N-CO-O- group, a ZO-CO-NZ- group, and a [or] Z_2N-CO-NZ- group; [,]

R_9 is selected from the group consisting of [represents] $COOR_{11}$, $SO(OR_{11})$, SO_3R_{11}, $P{=}O(OR_{11})_2$, $B(OR_{11})_2$, $P{=}OR_{11}(OR_{11})$, [or] tetrazole, and a [or any] carboxylic acid isostere; [,]

R_{10} is [represents] a  -group, [or] a  -group, or a  -group; [,]

[roup,]

R_{11} is [represents] H, C_1-C_6 alkyl, or aryl; [,]

R_{12} is [represents] C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group; [,]

R_{13} is [represents] H or C_1-C_6 alkyl; [,]

X is selected from the group consisting of [represents] O, S, SO, SO_2, $C(Z)_2$, N(Z), $NR_{13}SO_2$, SO_2NR_{13}, $NR_{13}CO$, and [or] $CONR_{13}$; [,]

Y is selected from the group consisting of [represents] O, N(Z), S, $C(Z)_2$, and [or] a single bond; and [,]

Z is [represents] independently selected from the group consisting of H, C_1-C_6 alkyl, aryl, cycloalkyl, and [or] heterocyclyl,

with the proviso that when X is [represents] O, S, SO, SO_2, N(Z), NR_7SO_2, SO_2NR_7, or NR_7CO, then Y is [represents] $C(Z)_2$ or a single bond.

8. The pharmaceutical formulation according to any one of claims 1-3 [previous claim], wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000 [, preferably from 50:1 to 1:50].

9. A kit of parts comprising:

(i) a vessel comprising [containing] an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof;

(ii) a vessel comprising [containing] a thrombin inhibitor, or a derivative thereof; and

(iii) instructions for the sequential, separate or simultaneous administration of the inhibitors (i) and (ii) to a patient in need thereof.

10. A [The] kit of parts [according to claim 9] comprising:

(i) a vessel comprising an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof;

(ii) a vessel comprising a thrombin inhibitor, or a derivative thereof; and

(iii) instructions for the sequential, separate, or simultaneous administration of the inhibitors (i) and (ii) to a patient in need thereof,

wherein the inhibitor of carboxypeptidase U is a compound according to [as defined in] claim 2

or 3.

11. The kit of parts according to claim[s] 9 [or 10], wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

15. The kit of parts according to claim 9 [any one of claims 9 to 14], wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000 [, preferably from 50:1 to 1:50].

16. A kit of parts comprising:

(i) a pharmaceutical formulation comprising [containing] an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier; and

(ii) a pharmaceutical formulation comprising [containing] a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier, [;]

wherein [which] inhibitors (i) and (ii) are each formulated [provided in a form that is suitable] for administration in conjunction with the other.

17. The kit of parts according to claim 16, wherein inhibitors (i) and (ii) are formulated [suitable] for sequential, separate or simultaneous administration.

18. A [The] kit of parts comprising [according to claim 16 or 17],

(i) a pharmaceutical formulation comprising an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier; and

(ii) a pharmaceutical formulation comprising a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier,

wherein inhibitors (i) and (ii) are each formulated for administration in conjunction with the other, and

wherein the inhibitor of carboxypeptidase U is a compound according to [as defined in] claim 2 or 3.

19. The kit of parts according to claim 16 or 17, [any one of claims 16 to 18], wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

23. The kit of parts according to claim 16 [any one of claims 16 to 22], wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000 [, preferably from 50:1 to 1:50].

25. A method for the treatment of a patient suffering from, or susceptible to, a condition in which inhibition of thrombin and/or inhibition of carboxypeptidase U are required or desired, which method comprises administering to the patient a therapeutically effective total amount of:
(i) an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and [in conjunction with]
(ii) a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier.

27. A [The] method [according to any one of claims 25 to 26] for the treatment of a patient suffering from, or susceptible to, a condition in which inhibition of thrombin and/or carboxypeptidase U are required or desired, which method comprises administering to the patient a therapeutically effective total amount of:
(i) an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier; and
(ii) a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent, or carrier,
wherein the inhibitor of carboxypeptidase U is a compound according to [as defined in] claim 2 or 3.

28. The method according to any one of claims 25 or 26 [to 27], wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

30. The method according to claim 29 [30], wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

32. The method according to claim 25 or 26 [any one of claims 25 to 31], wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000 [, preferably from 50:1 to 1:50].

33. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of thrombin and/or inhibition of carboxypeptidase U are required or desired, which method comprises administering to the patient a formulation according to [as defined in] any one of claims 1 to 3 [8].

CONCLUSION

Upon entry of this Preliminary Amendment, claims 1-23, 25-33, and 41-63 are pending. Applicants respectfully submit that claims 1-23, 25-33, and 41-63 are directed to patentable subject matter. Accordingly, Applicants request allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,

Andrew Fessak

Andrew Fessak
Reg. No. 48,528

Customer No. 07470
Direct Line: (212) 819-8437